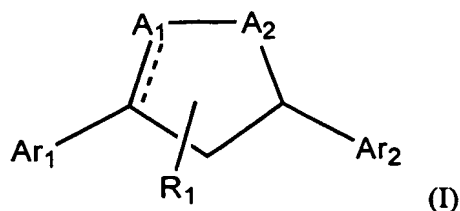


## CLAIMS

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

- Ar<sub>1</sub> and Ar<sub>2</sub> are independently a monocyclic six-member optionally substituted heteroaryl group;

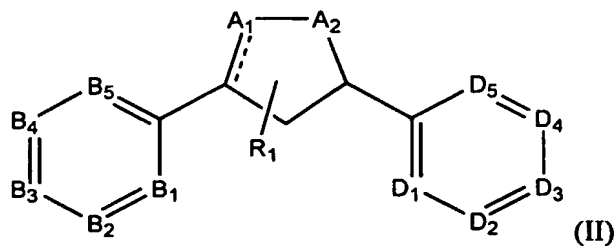
A<sub>1</sub> is =N- or -NR<sup>a</sup>- and A<sub>2</sub> is O or S;

R<sup>a</sup> is H or C1-C6 alkyl;

- R<sub>1</sub> is selected from -H, C1-C6 alkyl, phenyl, C1-C6 haloalkyl, halogen, -OH, -OR<sup>b</sup>, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, -O(C1-C6 haloalkyl), -SH, -SR<sup>b</sup>, -NO<sub>2</sub>, -CN, -NR<sup>b</sup>CO<sub>2</sub> R<sup>b</sup>, -NR<sup>b</sup>C(O) R<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -C(O)R<sup>b</sup>, -C(O)N(R<sup>b</sup>)<sub>2</sub>, -OC(O)R<sup>b</sup> and -NR<sup>b</sup>R<sup>b</sup>; and

each R<sup>b</sup> is H or a C1-C6 alkyl group.

2. The compound of Claim 1 represented by Formula (II):



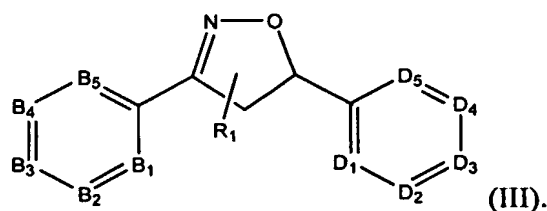
wherein:

B<sub>1</sub> through B<sub>5</sub> and D<sub>1</sub> through D<sub>5</sub> are independently N or CR<sup>c</sup>, provided that from one to three of B<sub>1</sub> through B<sub>5</sub> and from one to three of D<sub>1</sub> through D<sub>5</sub> are N;

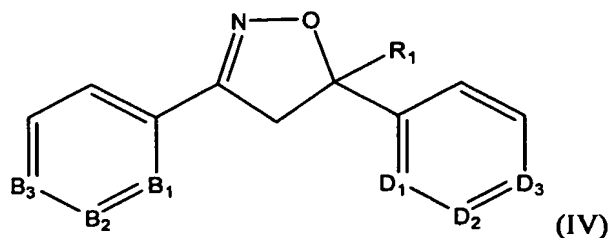
each R<sup>c</sup> is independently -H, C1-C6 alkyl, halogen, C1-C6 haloalkyl, -R<sup>o</sup>, -OH, -OR<sup>o</sup>, -O(C1-C6 haloalkyl), -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H, -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>, -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup>, -NHSO<sub>2</sub>R<sup>o</sup>, -N(R<sup>o</sup>)<sub>2</sub>, -NR<sup>o</sup>C(O)R<sup>o</sup>, or -C(O)N(R<sup>o</sup>)<sub>2</sub> or a C1-C6 alkyl group substituted with R<sup>o</sup>, -OH, -OR<sup>o</sup>, -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H, -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>, -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup>, -NHSO<sub>2</sub>R<sup>o</sup>; and

R<sup>o</sup> is independently, C1-C6 alkyl, aryl or heteroaryl group and wherein the aryl or heteroaryl group represented by R<sup>o</sup> is optionally substituted with one or more halogen, methyl or methoxy groups.

3. The compound of Claim 2 wherein the compound is represented by Formula (III):



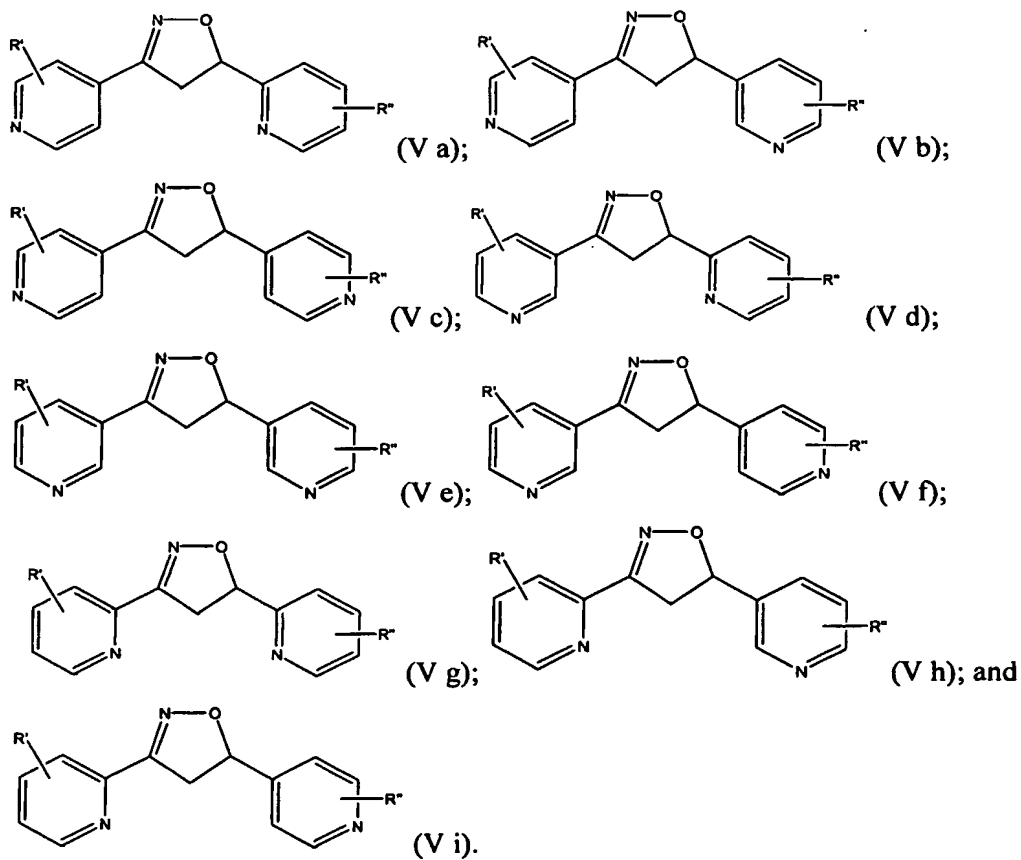
4. The compound of Claim 3 wherein the compound is represented by Formula (IV):



wherein one of B<sub>1</sub> through B<sub>3</sub> and one of D<sub>1</sub> through D<sub>3</sub> are N.

5. The compound of Claim 4 wherein  $R_1$  is -H or a C1-C3 alkyl optionally substituted with a halogen or a hydroxyl.
6. The compound of Claim 5 wherein
- 5  $R^c$  is -H, halogen,  $-\text{NO}_2$ ,  $-\text{CN}$ , C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl,  $-\text{N}(\text{R}^d)_2$ ,  $-\text{NR}^d\text{C}(\text{O})\text{R}^d$ , or  $-\text{C}(\text{O})\text{N}(\text{R}^d)_2$ ; and each  $\text{R}^d$  is H or a C1-C3 alkyl group.
7. The compound of Claim 6 selected from the group consisting of:

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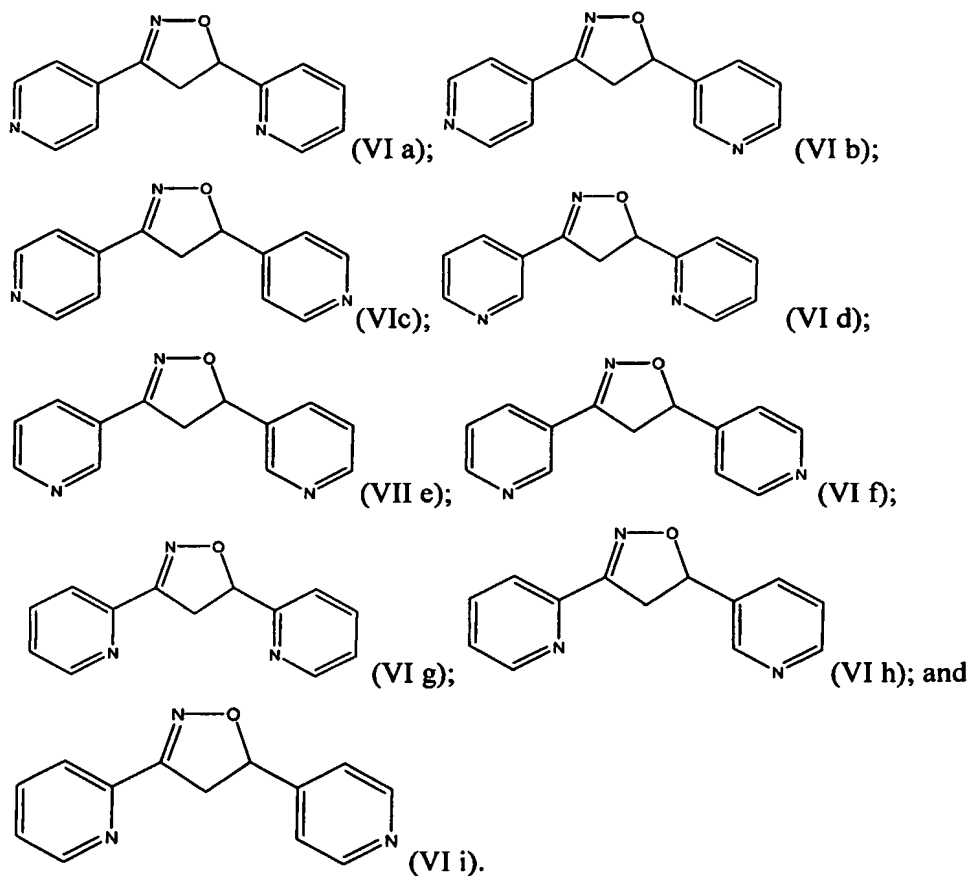


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wherein:

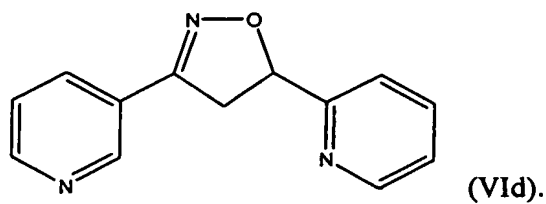
R' and R'' are independently -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, or -C(O)N(R<sup>d</sup>)<sub>2</sub>.

- 5    8.    The compound of Claim 7 selected from the group consisting of:



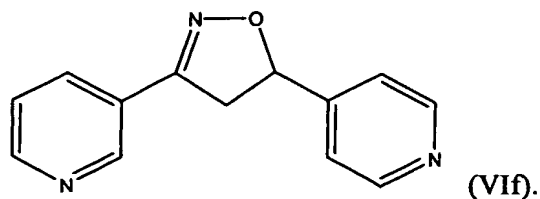
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9.    The compound of Claim 8 represented by Formula (VI d):

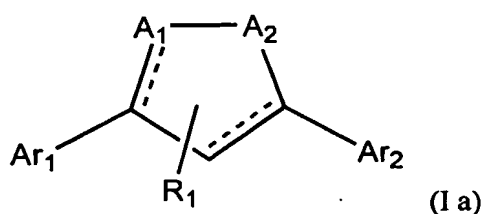


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10.    The compound of Claim 8 represented by Formula (VI f):



11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by Formula (I a) or a pharmaceutically acceptable salt thereof:



wherein:

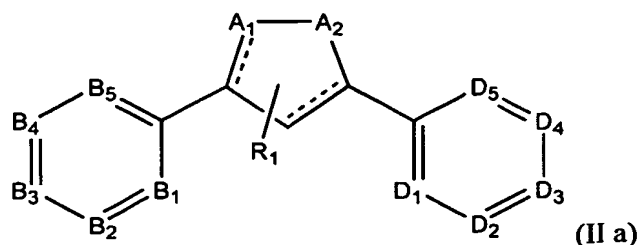
- Ar<sub>1</sub> and Ar<sub>2</sub> are independently a monocyclic six-member optionally substituted heteroaryl group;

A<sub>1</sub> is =N- or -NR<sup>a</sup>- and A<sub>2</sub> is O or S;

R<sup>a</sup> is H or C1-C6 alkyl;

- R<sub>1</sub> is selected from -H, C1-C6 alkyl, phenyl, C1-C6 haloalkyl, halogen, -OH, -OR<sup>b</sup>, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, -O(C1-C6 haloalkyl), -SH, -SR<sup>b</sup>, -NO<sub>2</sub>, -CN, -NR<sup>b</sup>CO<sub>2</sub> R<sup>b</sup>, -NR<sup>b</sup>C(O) R<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -C(O)R<sup>b</sup>, -C(O)N(R<sup>b</sup>)<sub>2</sub>, -OC(O)R<sup>b</sup> and -NR<sup>b</sup>R<sup>b</sup>; and each R<sup>b</sup> is H or a C1-C6 alkyl group.

12. The composition of Claim 11 wherein the compound is represented by Formula (II a):



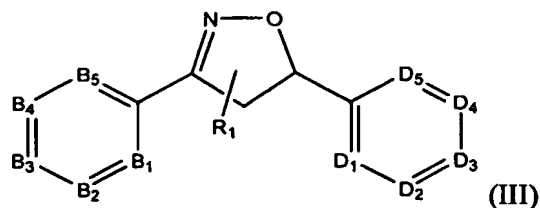
wherein:

B<sub>1</sub> through B<sub>5</sub> and D<sub>1</sub> through D<sub>5</sub> are independently N or CR<sup>c</sup>,  
 provided that from one to three of B<sub>1</sub> through B<sub>5</sub> and from one to three of  
 D<sub>1</sub> through D<sub>5</sub> are N;

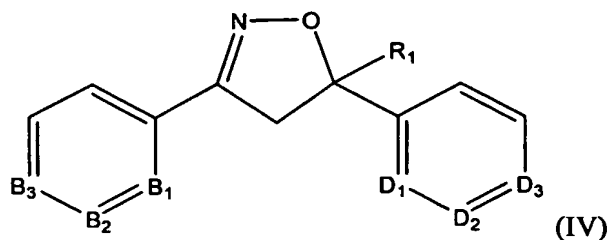
each R<sup>c</sup> is independently -H, C1-C6 alkyl, halogen, C1-C6  
 haloalkyl, -R<sup>o</sup>, -OH, -OR<sup>o</sup>, -O(C1-C6 haloalkyl), -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN,  
 -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H, -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>,  
 -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup>, -NHSO<sub>2</sub>R<sup>o</sup>,  
 -N(R<sup>o</sup>)<sub>2</sub>, -NR<sup>o</sup>C(O)R<sup>o</sup>, -C(O)N(R<sup>o</sup>)<sub>2</sub> or a C1-C6 alkyl group substituted  
 with R<sup>o</sup>, -OH, -OR<sup>o</sup>, -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H,  
 -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>, -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>,  
 -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup> or -NHSO<sub>2</sub>R<sup>o</sup>;

R<sup>o</sup> is independently C1-C6 alkyl, aryl or heteroaryl group and  
 wherein the aryl or heteroaryl group represented by R<sup>o</sup> is optionally  
 substituted with one or more halogen, methyl or methoxy groups.

13. The composition of Claim 12 wherein the compound is represented by Formula  
 (III):



14. The composition of Claim 13 wherein the compound is represented by Formula  
 (IV):



wherein one of B<sub>1</sub> through B<sub>3</sub> and one of D<sub>1</sub> through D<sub>3</sub> are N.

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15. The composition of Claim 14 wherein R<sub>1</sub> is -H or a C1-C3 alkyl optionally substituted with a halogen or a hydroxyl.

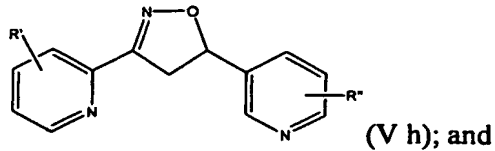
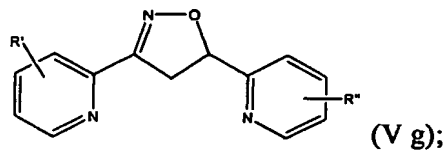
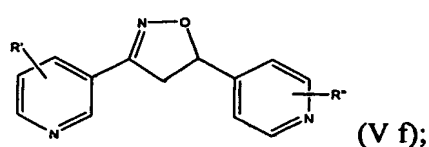
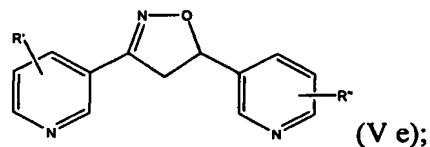
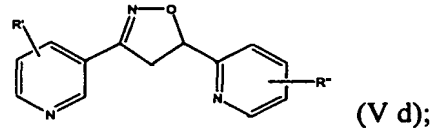
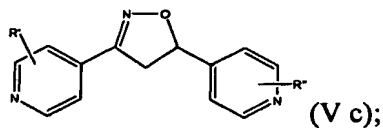
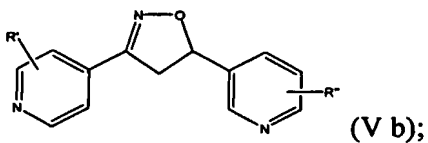
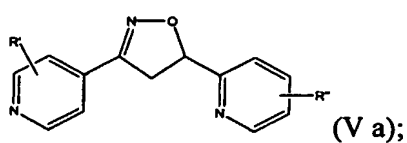
16. The composition of Claim 15 wherein

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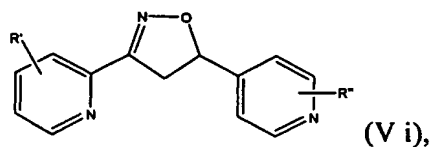
R<sup>c</sup> is -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl or C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, or -C(O)N(R<sup>d</sup>)<sub>2</sub>; and each R<sup>d</sup> is H or a C1-C3 alkyl group.

17. The composition of Claim 16 wherein the compound is selected from the group consisting of:

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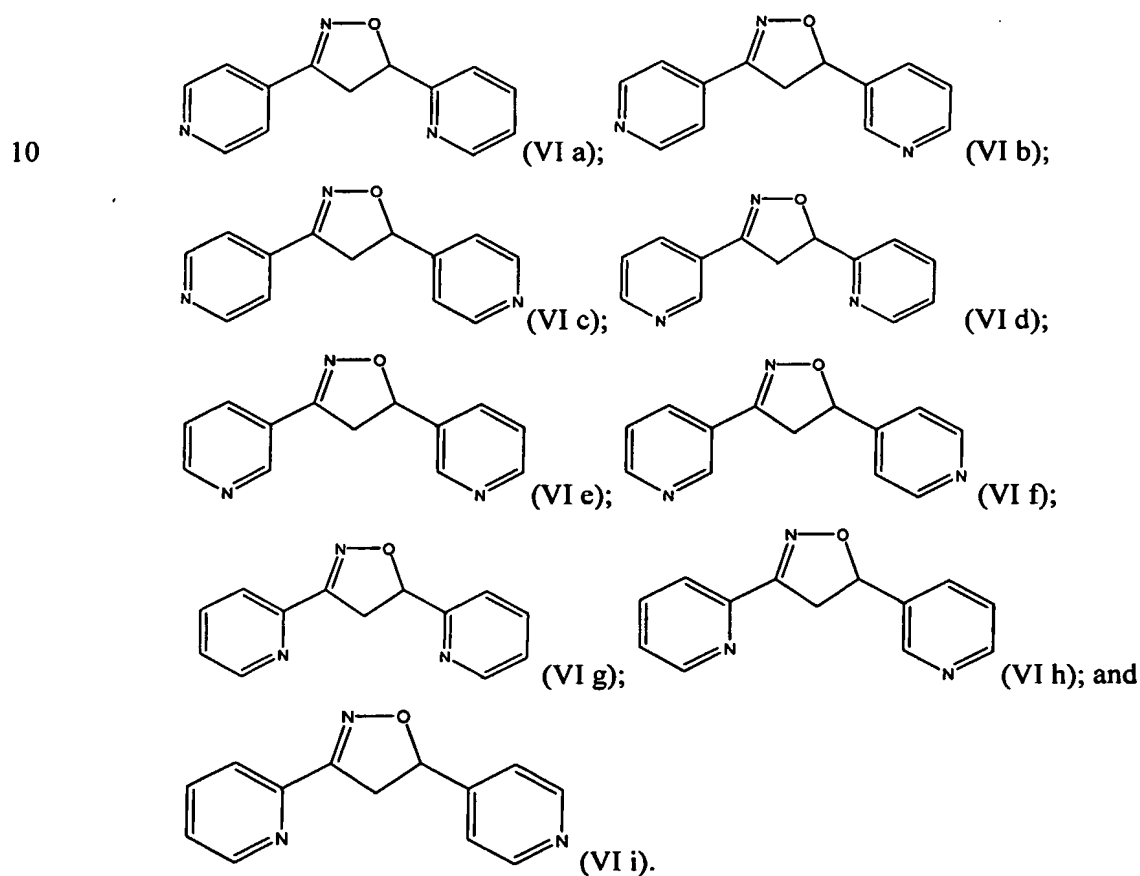
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wherein

- 5  $R'$  and  $R''$  are independently -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, or -C(O)N(R<sup>d</sup>)<sub>2</sub>.

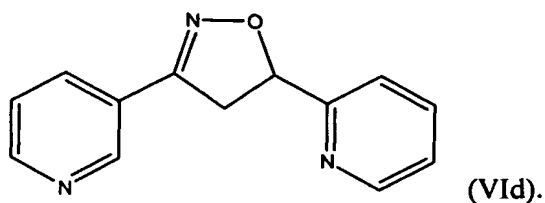
18. The composition of Claim 17 wherein the compound is selected from the group consisting of:



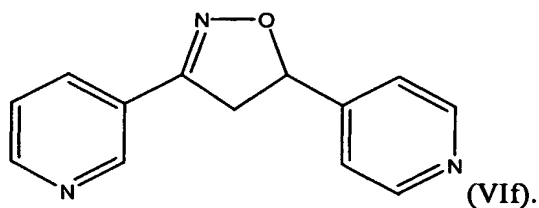
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19. The composition of Claim 18 wherein the compound is represented by Formula (VI d):

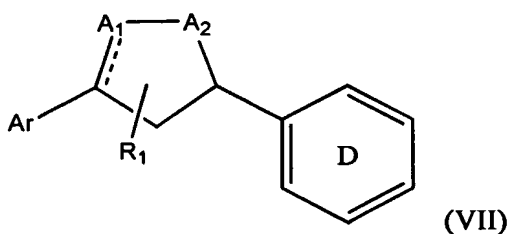




20. The composition of Claim 18 wherein the compound is represented by Formula (VI $\bar{f}$ ):



21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by Formula (VII) or a pharmaceutically acceptable salt thereof:



wherein:

Ar is an optionally substituted, monocyclic, six-member heteroaryl;

A<sub>1</sub> is =N- or -NR<sup>a</sup>- and A<sub>2</sub> is O or S;

R<sub>1</sub> is -H, C1-C6 alkyl, phenyl, C1-C6 haloalkyl, halogen, -OH, -OR<sup>b</sup>, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, -O(C1-C6 haloalkyl), -SH, -SR<sup>b</sup>, -NO<sub>2</sub>, -CN, -NR<sup>b</sup>CO<sub>2</sub> R<sup>b</sup>, -NR<sup>b</sup>C(O) R<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -C(O)R<sup>b</sup>, -C(O)N(R<sup>b</sup>)<sub>2</sub>, -OC(O)R<sup>b</sup> or -NR<sup>b</sup>R<sup>b</sup>;

each R<sup>a</sup> is -H or C1-C6 alkyl;

each R<sup>b</sup> is -H or a C1-C6 alkyl group; and

ring D is optionally substituted with zero, one or more substituents other than amide and is not an alkylphenol.

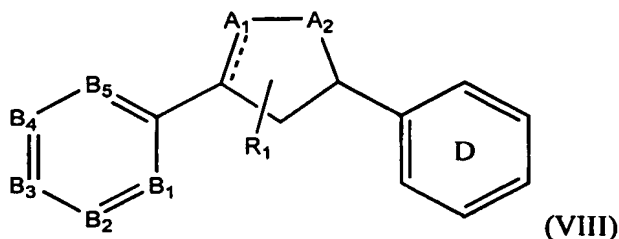
22. The pharmaceutical composition of Claim 21 wherein:

ring **D** is optionally substituted with zero, one or more substituents represented by  $R_2$ ;

5 each  $R_2$  is independently -H, halogen, C1-C6 haloalkyl,  $-R^0$ , -OH,  $-OR^0$ ,  $-O(C1-C6 \text{ haloalkyl})$ , -SH,  $-SR^0$ ,  $-NO_2$ , -CN,  $-NHCO_2R^0$ ,  $-NHC(O)H$ ,  $-NHC(O)R^0$ ,  $-CO_2H$ ,  $-CO_2R^0$ ,  $-C(O)H$ ,  $-C(O)R^0$ ,  $-OC(O)R^0$ ,  $-S(O)_2R^0$ ,  $-SO_2NH_2$ ,  $-S(O)R^0$ ,  $-NHSO_2R^0$ , or a C1-C6 alkyl group substituted with  $R^0$ , -OH,  $-OR^0$ , -SH,  $-SR^0$ ,  $-NO_2$ , -CN,  $-NHCO_2R^0$ ,  $-NHC(O)H$ ,  $-NHC(O)R^0$ ,  $-CO_2H$ ,  $-CO_2R^0$ ,  $-C(O)H$ ,  $-C(O)R^0$ ,  $-C(O)NHR^0$ ,  $-OC(O)R^0$ ,  $-S(O)_2R^0$ ,  $-SO_2NH_2$ ,  $-S(O)R^0$  or  $-NHSO_2R^0$ ;

$R^0$  is independently -H, C1-C6 alkyl, aryl or heteroaryl group wherein the aryl or heteroaryl group represented by  $R^0$  is optionally substituted with one or more halogen, methyl or methoxy groups.

23. The composition of Claim 22 wherein the compound is represented by Formula (VIII):



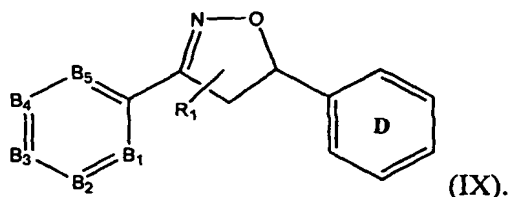
wherein:

$B_1$  through  $B_5$  are independently N or  $CR^c$ , provided that from one to three of  $B_1$  through  $B_5$  are N;

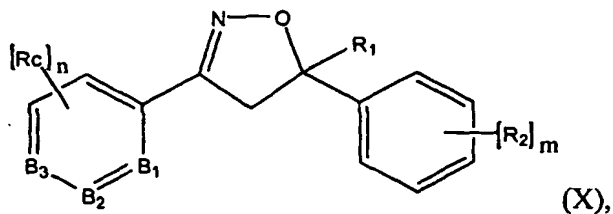
25 each  $R^c$  is independently -H, C1-C6 alkyl, halogen, C1-C6 haloalkyl,  $-R^0$ , -OH,  $-OR^0$ ,  $-O(C1-C6 \text{ haloalkyl})$ , -SH,  $-SR^0$ ,  $-NO_2$ , -CN,  $-NHCO_2R^0$ ,  $-NHC(O)H$ ,  $-NHC(O)R^0$ ,  $-CO_2H$ ,  $-CO_2R^0$ ,  $-C(O)H$ ,  $-C(O)R^0$ ,  $-C(O)NHR^0$ ,  $-OC(O)R^0$ ,  $-S(O)_2R^0$ ,  $-SO_2NH_2$ ,  $-S(O)R^0$ ,  $-NHSO_2R^0$ ,  $-N(R^0)_2$ ,  $-NR^0C(O)R^0$ ,  $-C(O)N(R^0)_2$  or a C1-C6 alkyl group substituted

with  $R^0$ , -OH, -OR<sup>0</sup>, -SH, -SR<sup>0</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>0</sup>, -NHC(O)H, -NHC(O)R<sup>0</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>0</sup>, -C(O)H, -C(O)R<sup>0</sup>, -C(O)NHR<sup>0</sup>, -OC(O)R<sup>0</sup>, -S(O)<sub>2</sub>R<sup>0</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>0</sup>, -NHSO<sub>2</sub>R<sup>0</sup>.

- 5 24. The pharmaceutical composition of Claim 23 wherein the compound is represented by formula (IX):



- 10 25. The composition of Claim 24 wherein the compound is represented by formula (X):



wherein:

- 15 one of B<sub>1</sub> through B<sub>3</sub> is N;  
 n is 0, 1 or 2; and  
 m is 0, 1 or 2.

- 20 26. The composition of Claim 25 wherein R<sub>1</sub> is -H or a C1-C3 alkyl optionally substituted with a halogen or a hydroxyl.

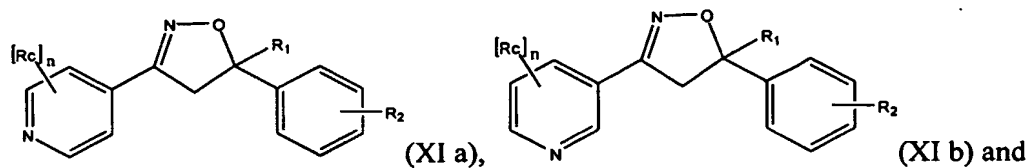
27. The composition of Claim 26 wherein:  
 each R<sub>2</sub> is independently -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl or C1-C3 alkoxyalkyl;

each  $R^c$  is independently -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, -C(O)N(R<sup>d</sup>)<sub>2</sub>; and

each  $R^d$  is H or a C1-C3 alkyl group.

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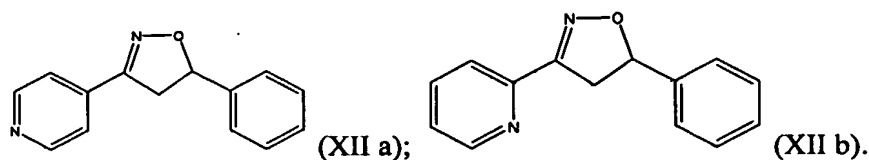
28. The composition of Claim 27 wherein the compound is selected from the group of:



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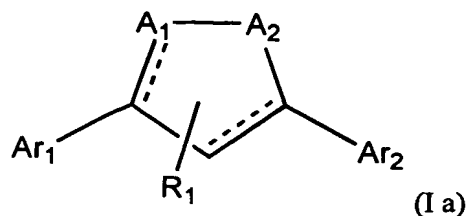
29. The pharmaceutical composition of Claim 28 wherein the compound is selected from the group consisting of:

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30. A method of treating a subject with an inflammatory cytokine mediated disorder comprising administering to the subject a therapeutically effective amount of a compound represented by Formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

Ar<sub>1</sub> and Ar<sub>2</sub> are independently monocyclic six-member optionally substituted heteroaryl groups;

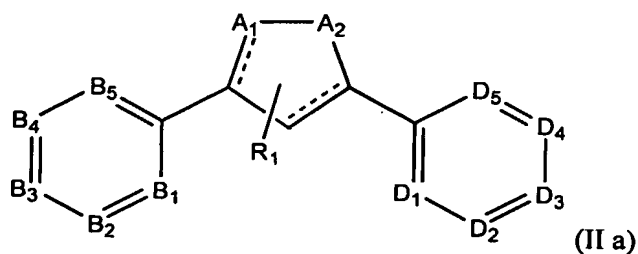
A<sub>1</sub> is =N- or -NR<sup>a</sup>- and A<sub>2</sub> is O or S;

R<sup>a</sup> is -H or C1-C6 alkyl;

R<sub>1</sub> is y selected from -H, C1-C6 alkyl, phenyl, C1-C6 haloalkyl, halogen, -OH, -OR<sup>b</sup>, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, -O(C1-C6 haloalkyl), -SH, -SR<sup>b</sup>, -NO<sub>2</sub>, -CN, -NR<sup>b</sup>CO<sub>2</sub> R<sup>b</sup>, -NR<sup>b</sup>C(O) R<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -C(O)R<sup>b</sup>, -C(O)N(R<sup>b</sup>)<sub>2</sub>, -OC(O)R<sup>b</sup> and -NR<sup>b</sup>R<sup>b</sup>; and

R<sup>b</sup> is -H or a C1-C6 alkyl group.

31. The method of Claim 30, wherein the compound is represented by Formula (II a):



wherein:

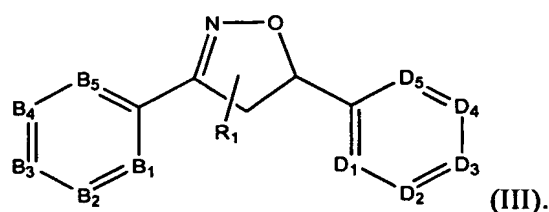
B<sub>1</sub> through B<sub>5</sub> and D<sub>1</sub> through D<sub>5</sub> are independently N or CR<sup>c</sup>, provided that from one to three of B<sub>1</sub> through B<sub>5</sub> and from one to three of D<sub>1</sub> through D<sub>5</sub> are N;

each R<sup>c</sup> is independently -H, C1-C6 alkyl, halogen, C1-C6 haloalkyl, -R<sup>o</sup>, -OH, -OR<sup>o</sup>, -O(C1-C6 haloalkyl), -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H, -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>,

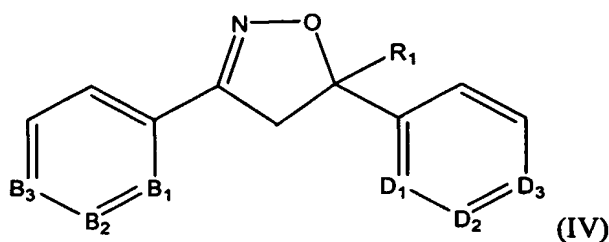
-C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup>, -NHSO<sub>2</sub>R<sup>o</sup>,  
 -N(R<sup>o</sup>)<sub>2</sub>, -NR<sup>o</sup>C(O)R<sup>o</sup>, -C(O)N(R<sup>o</sup>)<sub>2</sub> or a C1-C6 alkyl group substituted  
 with R<sup>o</sup>, -H, -OR<sup>o</sup>, -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H,  
 -NHC(O)R<sup>o</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>, -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>,  
 -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup> or -NHSO<sub>2</sub>R<sup>o</sup>; and

R<sup>o</sup> is independently C1-C6 alkyl, aryl or heteroaryl group and  
 wherein the aryl or heteroaryl group represented by R<sup>o</sup> is optionally  
 substituted with one or more halogen, methyl or methoxy groups.

32. The method of Claim 31 wherein the compound is represented by Formula (III):



33. The method of Claim 32 wherein the compound is represented by Formula (IV):



wherein one of B<sub>1</sub> through B<sub>3</sub> and one of D<sub>1</sub> through D<sub>3</sub> are N.

34. The method of Claim 33 wherein R<sub>1</sub> is -H or a C1-C3 alkyl, optionally substituted with a halogen or a hydroxyl.

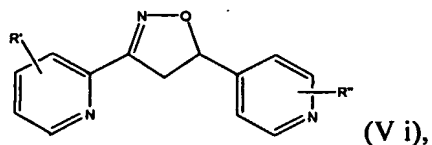
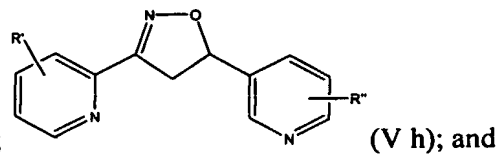
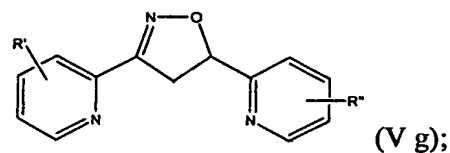
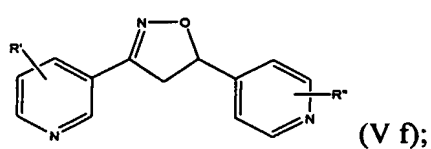
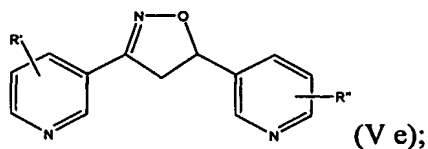
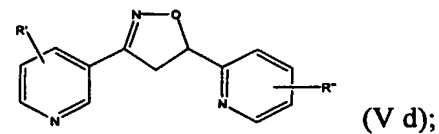
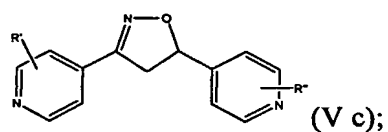
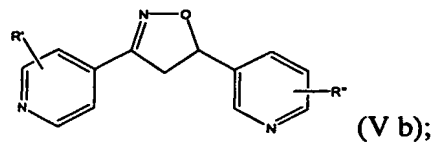
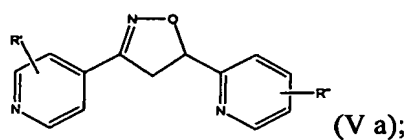
35. The method of Claim 34 wherein

R<sup>c</sup> is -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, -C(O)N(R<sup>d</sup>)<sub>2</sub>; and

each  $R^d$  is H or a C1-C3 alkyl group.

36. The method of Claim 35 wherein the compound is selected from the group consisting of:

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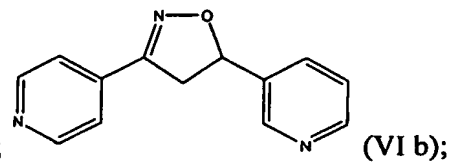
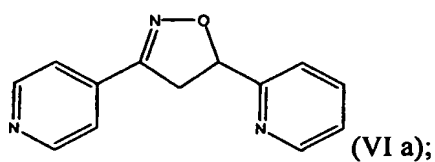
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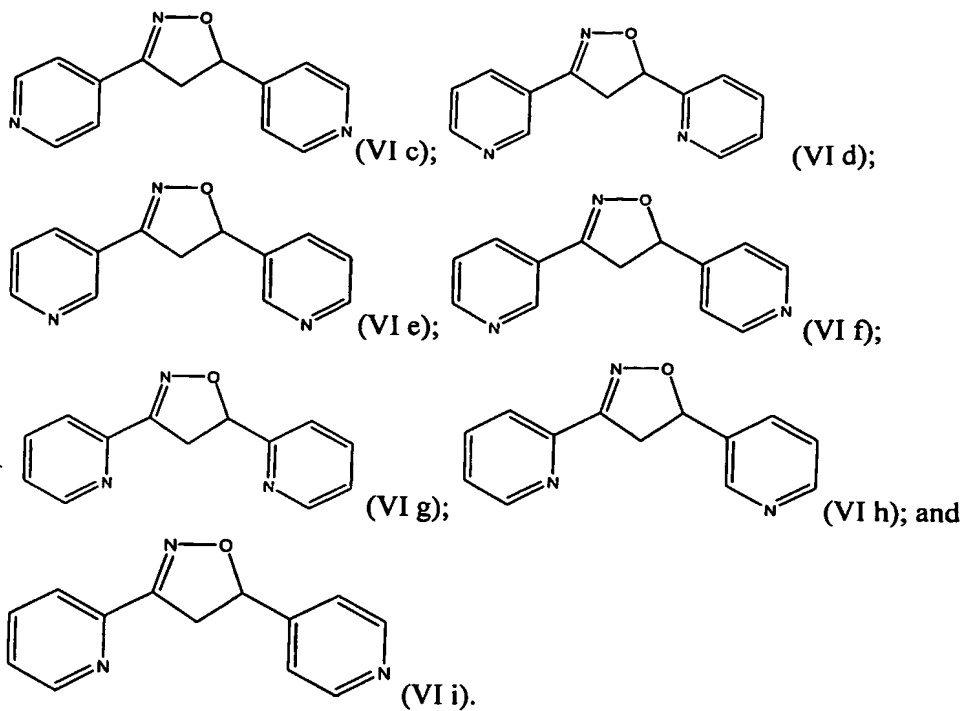
wherein

$R'$  and  $R''$  are independently -H, halogen,  $-NO_2$ , -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl,  $-N(R^d)_2$ ,  $-NR^dC(O)R^d$ ,  $-C(O)N(R^d)_2$ .

15

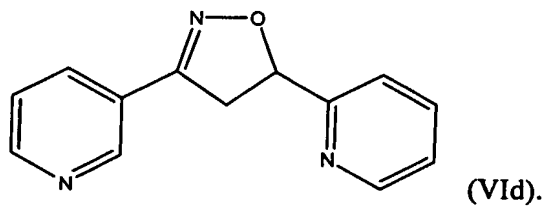
37. The method of Claim 36 wherein the compound is selected from the group consisting of:



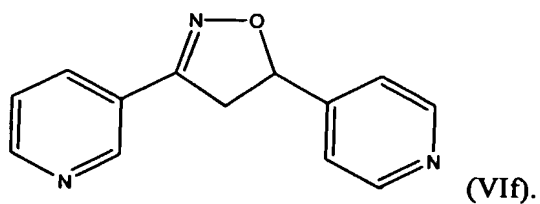


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38. The method of Claim 37 wherein the compound is represented by Formula (VI d):



- 10 39. The method of Claim 37 wherein the compound is represented by Formula (VI f):



40. The method of Claim 30 wherein the inflammatory cytokine is TNF- $\alpha$  or HMGB-1.

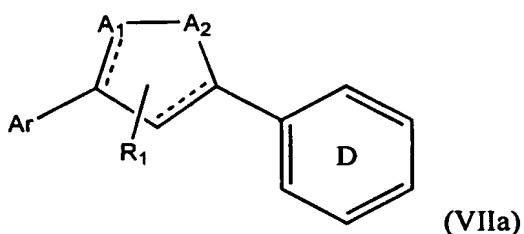
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41. The method of Claim 40 wherein the disorder is selected from the group consisting of appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute or ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, asthma, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis, pneumoultramicroscopic silicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria, warts, wheals, vasculitis, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillame-Barre syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcets's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Type I diabetes, ankylosing spondylitis, Retier's syndrome, or Hodgkins disease. In more preferred embodiments, the condition is appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute or ischemic colitis, hepatitis, Crohn's disease, asthma, allergy, anaphylactic shock, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory

distress syndrome, cerebral infarction, cerebral embolism, spinal cord injury, paralysis, allograft rejection and graft-versus-host disease.

42. The method of Claim 41 wherein the disorder is selected from the group consisting of peritonitis, pancreatitis, ulcerative colitis, Crohn's disease, asthma, organ ischemia, reperfusion ischemia, sepsis, cachexia, burns, myocardial ischemia, adult respiratory distress syndrome, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, chronic obstructive pulmonary disease, psoriasis, Behcet's syndrome, allograft rejection and graft-versus-host disease.
43. The method of Claim 42 wherein the disorder is sepsis.
44. A method of treating a subject with an inflammatory cytokine mediated disorder comprising administering to the subject a therapeutically effective amount of a compound represented by Formula (VIIa) or a pharmaceutically acceptable salt thereof:



wherein

- Ar is an optionally substituted, monocyclic, six-member heteroaryl;  
 $A_1$  is =N- or -NR<sup>a</sup>- and  $A_2$  is O or S;  
 $R_1$  is -H, C1-C6 alkyl, phenyl, C1-C6 haloalkyl, halogen, -OH, -OR<sup>b</sup>, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, -O(C1-C6 haloalkyl), -SH, -SR<sup>b</sup>, -NO<sub>2</sub>, -CN, -NR<sup>b</sup>CO<sub>2</sub> R<sup>b</sup>, -NR<sup>b</sup>C(O) R<sup>b</sup>, -CO<sub>2</sub>R<sup>b</sup>, -C(O)R<sup>b</sup>, -C(O)N(R<sup>b</sup>)<sub>2</sub>, -OC(O)R<sup>b</sup> or -NR<sup>b</sup>R<sup>b</sup>;  
 each R<sup>a</sup> is -H or C1-C6 alkyl group;  
 each R<sup>b</sup> is -H or a C1-C6 alkyl group;

ring **D** is optionally substituted with zero, one or more substituents other than amide and is not an alkylphenol.

45. The pharmaceutical composition of Claim 44 wherein

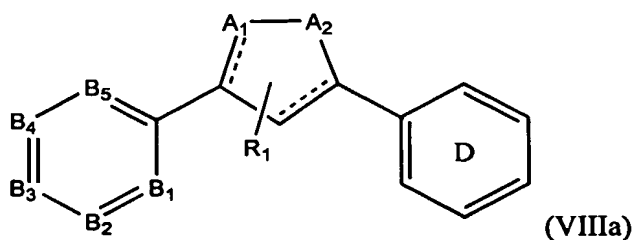
5 ring **D** is optionally substituted with zero, one or more substituents represented by  $R_2$ ;

each  $R_2$  is independently -H, a halogen, C1-C6 haloalkyl,  $-R^\circ$ , -OH,  $-OR^\circ$ , -O(C1-C6 haloalkyl), -SH,  $-SR^\circ$ ,  $-NO_2$ , -CN,  $-NHCO_2R^\circ$ ,  $-NHC(O)H$ ,  $-NHC(O)R^\circ$ ,  $-CO_2H$ ,  $-CO_2R^\circ$ ,  $-C(O)H$ ,  $-C(O)R^\circ$ ,  $-OC(O)R^\circ$ ,  $-S(O)_2R^\circ$ ,  $-SO_2NH_2$ ,  $-S(O)R^\circ$ ,  $-NHSO_2R^\circ$ , or a C1-C6 alkyl group substituted with  $R^\circ$ , -OH,  $-OR^\circ$ , -SH,  $-SR^\circ$ ,  $-NO_2$ , -CN,  $-NHCO_2R^\circ$ ,  $-NHC(O)H$ ,  $-NHC(O)R^\circ$ ,  $-CO_2H$ ,  $-CO_2R^\circ$ ,  $-C(O)H$ ,  $-C(O)R^\circ$ ,  $-C(O)NHR^\circ$ ,  $-OC(O)R^\circ$ ,  $-S(O)_2R^\circ$ ,  $-SO_2NH_2$ ,  $-S(O)R^\circ$  or  $-NHSO_2R^\circ$ , and

15  $R^\circ$  is independently -H, C1-C6 alkyl, aryl or heteroaryl group wherein the aryl or heteroaryl group represented by  $R^\circ$  is optionally substituted with one or more halogen, methyl or methoxy groups.

46. The method of Claim 45 wherein the compound is represented by Formula (VIIIa):

20



wherein:

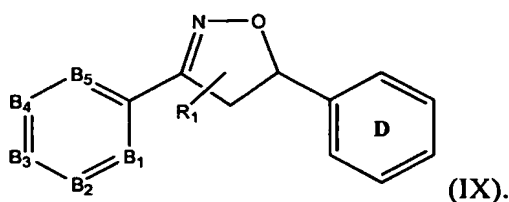
25  $B_1$  through  $B_5$  are independently N or  $CR^c$ , provided that from one to three of  $B_1$  through  $B_5$  are N;

each  $R^c$  are independently -H, halogen, C1-C6 haloalkyl,  $-R^\circ$ , -OH,  $-OR^\circ$ , -O(C1-C6 haloalkyl), -SH,  $-SR^\circ$ ,  $-NO_2$ , -CN,  $-NHCO_2R^\circ$ ,  $-NHC(O)H$ ,  $-NHC(O)R^\circ$ ,  $-CO_2H$ ,  $-CO_2R^\circ$ ,  $-C(O)H$ ,  $-C(O)R^\circ$ ,  $-C(O)NHR^\circ$ ,

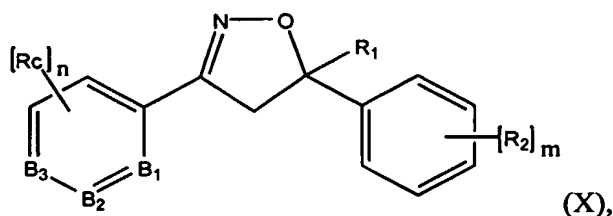
-OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup>, -NHSO<sub>2</sub>R<sup>o</sup>, -N(R<sup>o</sup>)<sub>2</sub>,  
 -NR<sup>o</sup>C(O)R<sup>o</sup>, -C(O)N(R<sup>o</sup>)<sub>2</sub> or a C1-C6 alkyl group substituted with R<sup>o</sup>,  
 -OH, -OR<sup>o</sup>, -SH, -SR<sup>o</sup>, -NO<sub>2</sub>, -CN, -NHCO<sub>2</sub>R<sup>o</sup>, -NHC(O)H, -NHC(O)R<sup>o</sup>,  
 -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>o</sup>, -C(O)H, -C(O)R<sup>o</sup>, -C(O)NHR<sup>o</sup>, -OC(O)R<sup>o</sup>, -S(O)<sub>2</sub>R<sup>o</sup>,  
 -SO<sub>2</sub>NH<sub>2</sub>, -S(O)R<sup>o</sup> or -NHSO<sub>2</sub>R<sup>o</sup>; and

R<sup>o</sup> is independently -H, C1-C6 alkyl, aryl or heteroaryl group  
 wherein the aryl or heteroaryl group represented by R<sup>o</sup> is optionally  
 substituted with one or more halogen, methyl or methoxy groups.

47. The method of Claim 46 wherein the compound is represented by formula (IX):



48. The method of Claim 47 wherein the compound is represented by formula (X):



wherein

one of B1 through B3 is N;

n is 0, 1 or 2; and

m is 0, 1 or 2.

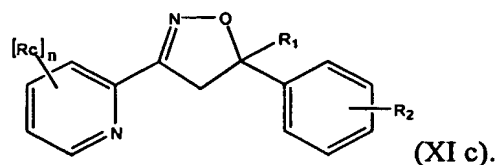
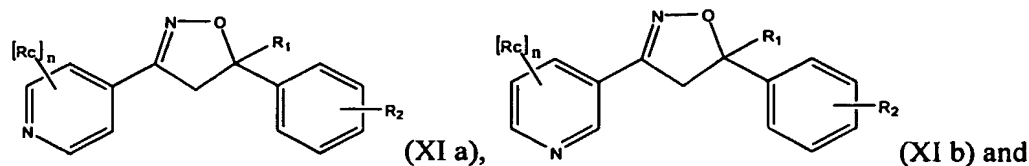
49. The composition of Claim 48 wherein R<sub>1</sub> is -H or a C1-C3 alkyl optionally  
 substituted with a halogen or a hydroxyl.

50. The method of Claim 49 wherein:

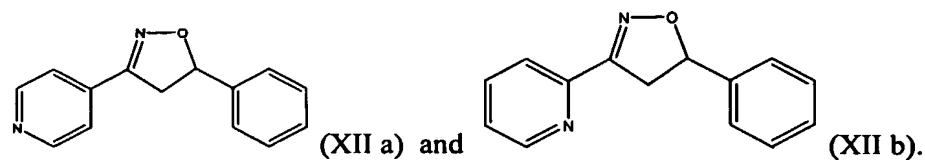
each  $R^c$  and each  $R_2$  are independently -H, halogen, -NO<sub>2</sub>, -CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 hydroxyalkyl, C1-C3 alkoxyalkyl, -N(R<sup>d</sup>)<sub>2</sub>, -NR<sup>d</sup>C(O)R<sup>d</sup>, -C(O)N(R<sup>d</sup>)<sub>2</sub>; and

5 each R<sup>d</sup> is H or a C1-C3 alkyl group.

51. The method of Claim 50 wherein the compound is selected from the group of:



52. The method of Claim 51 wherein the compound is selected from the group consisting of:



53. The method of Claim 44 wherein the inflammatory cytokine is TNF- $\alpha$  or HMGB-1.

54. The method of Claim 53 wherein the disorder is selected from the group consisting of appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute or ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, asthma, allergy, anaphylactic shock, immune

- complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis,
- 5 pneumoultramicroscopic silicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria,
- 10 warts, wheals, vasculitis, angitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillame-Barre syndrome,
- 15 neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcets's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Type I
- 20 diabetes, ankylosing spondylitis, Retier's syndrome, or Hodgkins disease. In more preferred embodiments, the condition is appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute or ischemic colitis, hepatitis, Crohn's disease, asthma, allergy, anaphylactic shock, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia,
- 25 endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, cerebral infarction, cerebral embolism, spinal cord injury, paralysis, allograft rejection and graft-versus-host disease.
- 30 55. The method of Claim 54 wherein the disorder is selected from the group consisting of peritonitis, pancreatitis, ulcerative colitis, Crohn's disease, asthma, organ ischemia, reperfusion ischemia, sepsis, cachexia, burns, myocardial

ischemia, adult respiratory distress syndrome, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, chronic obstructive pulmonary disease, psoriasis, Behcet's syndrome, allograft rejection and graft-versus-host disease.

- 5    56.    The method of Claim 55 wherein the disorder is sepsis.